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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Elizabeth M. Denholm, Yong-Qing Lin and Paul J. Silver

Serial No.: 09/715,965

Art Unit: 1654

Filed: November 17, 2000

Examiner: Michael Meller

For: *ATTENUATION OF TUMOR GROWTH, METASTASIS AND ANGIOGENESIS*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO EXAMINER'S ANSWER

Sir:

This is a reply to the examiner's answer mailed May 18, 2004 in the above-identified application. Enclosed with this Reply is a Request for Oral Hearing and a request to charge the appropriate fee of \$290.00 for a large entity. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

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REPLY TO EXAMINER'S ANSWER**(4) STATUS OF AMENDMENTS**

The claims were last amended in the amendment mailed on October 17, 2003. In the Advisory Action mailed on December 11, 2003, the Examiner indicated that the amendment would be entered. Appendix I sets forth the claims on appeal.

An amendment waenclosed with the appeal brief to correct antecedent basis. Appendix II sets forth the proposed amended claims.

The Examiner has not indicated whether or amendment filed with the Appeal Brief will be entered. Assuming entry, the claims on appeal are those found in Appendix II of the Appeal Brief.

(6) ISSUES ON APPEAL

The issues presented on appeal are:

- (1) whether claims 1-11 and 19-27 are enabled as required by 35 U.S.C. § 112, first paragraph;
- (2) whether claims 1-11 and 19-27 are sufficiently described as required by 35 U.S.C. § 112, first paragraph;
- (3) whether claims 1-11 and 19-27 are definite under 35 U.S.C. § 112, second paragraph;
- (4) whether claims 1, 2, 4-6 and 8 lack novelty under 35 U.S.C. § 102(b) over U.S. Patent No. 4,696,816 to Brown ("Brown");

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(5) whether claims 1, 2, 4, 5, 9, 10 and 27 lack novelty under 35 U.S.C. § 102(b) over Takeuchi, *Br J Cancer* 26, 115 (1972) ("Takeuchi");

(6) whether claims 1-5, 8-11, 24, 25 and 27 lack novelty under 35 U.S.C. § 102(b) over WO 96/01648 to Ibex Technologies, Inc ("Ibex");

(7) whether claims 1-11 and 19-27 are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,567,417 to Sasisekharan, et al. in view of Takeuchi, Brown or Ibex.

(8) whether claims 1-11 and 19-27 are obvious under 35 U.S.C. § 103(a) over Takeuchi, Brown or Ibex.

(7) GROUPING OF CLAIMS

It appears that the undersigned and examiner agree the claims do not stand or fall together, even if for different reasons.

(8) ARGUMENTS

There appear to be no additional arguments relating to the rejections of claims 1-11 and 19-27 Under 35 U.S.C. § 112, first paragraph enablement and written description. The examiner has not responded to the evidence provided by the appellants with respect to angigenic based disease.

The claims are definite as required by 35 U.S.C. § 112, second paragraph

The examiner has rejected claims 1-11 and 19-27 as indefinite for use of the phrase "an established disorder requiring angiogenesis".

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The sufficiency of the description, enablement of the claims, and the understanding of one skilled in the art with respect to this phrase was discussed in the appeal brief. As stated in the Appeal Brief, angiogenesis is a process whereby new blood vessels form. This is essential in normal development, especially of the fetus, in wound repair, and in weight gain (growth of adipose tissue). It is also essential in some diseases and disorders. The role angiogenesis plays has become of such importance that there is not only a great deal of research in the field to understand the process, but also of inhibitors and growth factors. Copies of the pages from the Angiogenesis Foundation's webpage are enclosed with the Appeal Brief to demonstrate the common knowledge regarding this process and the disorders and disease where it is known that angiogenesis plays a major role.

One major area of interest involves tumors. Tumor metastasis is the process by which malignant cancer cells escape from a tumor and spread throughout the body to develop into multiple secondary tumors. Escape from the primary tumor and invasion into other organs is a complex multi-step process. Metastasis involves changes in tumor cell adhesion and motility, secretion of proteolytic enzymes, chemoattractants and proteoglycans. Angiogenesis is also a vital step in the metastatic process. Agents that inhibit angiogenesis have been shown to be effective in inhibiting growth of tumors.

Angiogenesis involves the proliferation and migration of normal endothelial cells, not tumor cells. Appellants have shown that a highly purified and specific glycosaminoglycan

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degrading enzyme chondroitinase AC and, to a lesser extent chondroitinase B, can be used to inhibit angiogenesis by inhibiting endothelial cell migration and proliferation. This is demonstrated using well accepted *in vitro* and *in vivo* models of angiogenesis. The enzymatic removal of chondroitin sulfates A and C, and to a lesser extent, chondroitin sulfate B, decreases angiogenesis by inhibiting both endothelial cell proliferation and capillary formation.

Decreasing the formation of new blood vessels effectively inhibits angiogenesis, which in turn effectively treats disorders which are dependent on angiogenesis. Representative disorders that are angiogenic dependent are described on pages 10 and 11.

Example 5 demonstrates that chondroitinase AC inhibits endothelial cell proliferation in a dose dependent manner (see Figure 7). Example 6 demonstrates that chondroitinase inhibits angiogenesis, measured as inhibition of capillary-like structures, in a dose-dependent manner (see Figure 5). The remaining examples demonstrate that chondroitinases can be used to inhibit tumor cell proliferation and migration. At the time this application was filed, with priority to November 1999, it was not known that enzymes that cleave chondroitin sulfates could be used to inhibit *angiogenesis*. It was not known that enzymes that could cleave chondroitin sulfates could inhibit tumor cell proliferation or migration in a dose-dependent manner. It is this discovery that appellants made that forms the basis of the claimed methods.

Claim 1 is even more specific by requiring:

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Administering to a site in an individual in need of treatment thereof for an established disorder requiring angiogenesis an effective amount of a purified chondroitinase to decrease angiogenesis at the site,

Wherein the decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of capillary-like structures. (emphasis added)

The language at issue is "an established disorder requiring angiogenesis". Disorders requiring angiogenesis are listed on pages 10-11 of the specification. Metastasis of an established tumor is described on page 1, line 22 to page 2, line 3 as requiring angiogenesis. A tumor larger than 2-3 mm³ requires angiogenesis to supply nutrients to the tumor. Thus, once a tumor is palpable or large enough to break through the basal lamina and enter the bloodstream, it is established in the host. On page 10, line 8 it states that chondroitinases are used "to inhibit formation, growth and/or metastasis if tumors." In order to inhibit growth and/or metastasis of a tumor, the tumor first needs to be established. If a tumor is not established, it can not grow or metastasize. Similarly on page 6, lines 11-14 the actions of chondroitinase AC and chondroitinase B regulate tumor growth and metastasis by decreasing endothelial cell proliferation and capillary formation and thereby reducing tumor cell access to the bloodstream.

Example 6 on page 17 of the specification describes the inhibition of growth of capillary-like structures in an *in vitro* angiogenesis assay after treatment with chondroitinase AC.

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Example 9 on page 19 describes the treatment of a mouse with cancer, an established disorder characterized by palpable tumors, with chondroitinase AC. The examples of the specification demonstrate that at the time of filing, the Appellants were in possession of the claimed invention.

One skilled in the art would therefore have no trouble understanding the meaning of the claim language.

With respect to claim 2, it is believed that the claim language is grammatically correct.

With respect to the phrase "wherein these enzymes are expressed from recombinant nucleotide sequences in bacteria", it is believe one skilled in the art would know that the enzymes referred to in claim 2 are normally expressed by the named bacteria, but that since all of these enzymes have been cloned, one could also express the same nucleotide molecule in a different organism. The amino acid sequence should be the same, but the bacteria expressing the enzyme would be different. Accordingly, there could be some minor differences in contaminants or phosphorylation, but otherwise the enzymes would be the same whether isolated from the natural source or recombinant. See pages 6-7 of the application.

Rejections Under 35 U.S.C. § 102

The prior art rejections in the examiner's answer appear to be identical to the rejections in the last office action. No response to appellant's arguments have been provided.

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With respect to Brown, it appears that examiner has also acknowledged that Brown relates to treatment of cartilage based disorders. There is no connection between the reference to tumors and a method of treatment, even less so a specific teaching of how to treat tumors.

With respect to Takeuchi, it is clear that the enzyme is administered with the tumors.

Newly injected tumors do not have a blood supply – this takes weeks to establish. Therefore, whatever effect Takeuchi observed, it was not based on inhibition of angiogenesis of an established blood tumor into the tumors, but to some other effect, possibly relating to the ability of the tumors to implant or be rejected and killed by the immune system. Therefore the method is not inherently the same as what is being claimed, and one skilled in the art would not be led by Takeuchi's observation of tumorcidal activity following simultaneous injection of tumors and enzyme, to expecting injection of enzyme much later, filing establishment of the tumors, to have a reasonable expectation that such treatment would be successful.

With respect to Sasisekaran, the examiner has still provided no basis for why one skilled in the art would extrapolate from a reference about heparinases to the use of chondroitinases – except by hindsight analysis of appellants' application. The two enzymes have different origins, different amino acid sequences, different substrate specificities, and no evidence has been provided that one would expect to be able to substitute a chondroitinase for a heparinase, much less how much or when.

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For the foregoing reasons, Appellant submits that the claims 1-11 and 19-27 are patentable.

Respectfully submitted,



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